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Cognitive Interventions Targeting Executive Functions

How Do They Impact Prefrontal Circuits?

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Abstract

Executive functions (EFs) are essential for everyday functioning. Implicated in many neurodevelopmental and psychiatric disorders, they are also highly susceptible to the effects of aging. There is a critical need to develop effective interventions to improve EFs. This chapter focuses on a particular type of intervention that directly targets EFs by repeatedly practicing on EF tasks using adaptive procedures. There is emerging evidence that such interventions are beneficial: not only do they improve skills related to the trained domain, but they also benefit other domains and symptoms as well as lead to changes in brain structure and function, especially in circuitry related to the prefrontal cortex. At the same time, little is known about the exact underlying mechanisms that drive behavioral and neural changes. Thus, a better understanding of individual differences and training-related factors that mediate and moderate training outcomes is needed to develop more effective interventions that take into account individuals' strengths and needs.

The Malleability of Executive Functions

Extensive research has demonstrated the malleability of executive functions (EFs) and related cognitive functions that rely on the integrity of the prefrontal circuits, demonstrating that these cognitive functions are susceptible to the effects of development and experience (Hsu et al. 2014; Mackey et al. 2013; Zelazo and Carlson 2020). Capitalizing on the plasticity of these circuits, there has been an increasing interest in interventions to remediate, improve, or maintain cognitive functions across the lifespan (Salmi et al. 2018; Tullo and Jaeggi 2022). Many cognitive interventions consist of repeated practice on a task or several tasks that target specific aspects of cognition, with

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the idea that this practice results in improvements not only in the targeted cognitive function but also translates to other domains related to the trained domain (Pahor et al. 2018). Although many types of cognitive interventions have been shown to impact prefrontal cortex (PFC) circuitry, including goal management therapy (e.g., Stamenova and Levine 2019) and other types of cognitive rehabilitation and remediation (e.g., Geraldo et al. 2023; Vita et al. 2021), we focus here on interventions which more narrowly and directly target EFs and related functions, such as working memory (WM). Typically, these types of interventions involve repeated practice on computerized EF tasks and are often referred to as "brain training" (e.g., Pahor et al. 2018). We note that our primary focus is on cognitive outcomes and their neural correlates, while acknowledging that outcomes which focus on social cognition, metacognitive processes, affect regulation, or self-control are equally important. The latter are, however, beyond the scope of this review; for further information see, for example, Course-Choi et al. (2017), du Toit et al. (2020), Philipp et al. (2019), Tang et al. (2022b), Vickery and Dorjee (2016), and Webb et al. (2012).

As illustrated elsewhere in this volume, EFs refer to a multidimensional construct that includes a set of cognitive mechanisms that control and regulate the contents of WM and action (cf. Murray and Constantinidis, this volume), as well as the ability to plan steps to a problem, ignore distracting information, monitor performance, override automatic responses, or control impulses and regulate emotions (Hsu and Jaeggi 2014). Overall, EFs facilitate purposeful and goal-directed behavior, which is especially critical in novel situations or tasks that have not been well learned (Norman and Shallice 1986). Not surprisingly, EFs are important for everyday life functions in that they predict school readiness, scholastic achievement, job productivity, and even physical health and quality of life (cf. Table 1 in Diamond 2013). EFs are also critically impaired in a range of clinical syndromes, such as depression, attention-deficit hyperactivity disorder (ADHD), addiction, and schizophrenia (Jones and Graff-Radford 2021). The development of EFs follows a distinct, inverted U-shaped trajectory across the human lifespan, typically yielding the best performance at young adulthood, followed by a gradual decline with aging (Hartshorne and Germine 2015). Although the structure of EFs and the extent to which the structure changes across the lifespan is still being debated (Karr et al. 2018), the most popular and well-established models explicate three primary subdomains that are intercorrelated—WM/updating, inhibition, and cognitive flexibility—each of which relies on distinct neural networks (Friedman and Miyake 2017; Friedman and Robbins 2022; cf. other chapters in this volume).

Given their relevance for cognitive and brain health across the lifespan, approaches to strengthen EF skills have appealed to many scientists and practitioners. It has been argued that strengthening specific EFs with targeted training might increase the efficacy of PFC circuitry functioning (Constantinidis and Klingberg 2016), and consequentially lead to performance benefits in

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domains that rely on the integrity of PFC functioning, especially if trained and nontrained tasks rely on overlapping neural circuitry (Bäckman et al. 2011; Salmi et al. 2018; Vartanian et al. 2022). Indeed, there is growing evidence that targeted, mostly computerized, EF training can improve performance in closely related domains ("near transfer"); this has been demonstrated in various clinical and nonclinical populations across the lifespan (Tullo and Jaeggi 2022). There are, however, persistent inconsistencies and controversies about whether and to what extent such targeted training reliably impacts cognitive functions beyond the trained domain or real-world behavior, such as success in school or ADHD symptoms ("far transfer"): several meta-analyses have demonstrated small effects (Au et al. 2015; Karbach and Verhaeghen 2014; Soveri et al. 2017) while others argue that such findings are essentially noise (Melby-Lervåg et al. 2016; Sala et al. 2019).

Our own view is more optimistic. We suggest that the inconsistency in results and controversy reflect not only the heterogeneity of EF training implementation, choice of outcome measures (Pergher et al. 2020b), and issues with measurement (Karr et al. 2018; Yangüez et al. 2023) but also variability across participants (Pahor et al. 2022). Importantly, those issues do not undermine the potential for EF training to improve cognitive and brain health. Instead, our groups argue that current research should focus on identifying and evaluating the underlying cognitive and neural mechanisms, as well as determine individual differences—the mediating and moderating factors that impact training efficacy (Jaeggi et al. 2011; Pahor et al. 2022)—using appropriate and evidence-based methodology (Green et al. 2019).

Critically, targeted EF training has provided new knowledge of how prefrontal circuits respond to experience and repeated practice using a causal approach and, as such, has contributed to a better understanding of brain plasticity and underlying mechanisms of learning across the lifespan. What makes targeted and computerized EF training particularly well suited to investigate brain plasticity in humans is that it relies on well-defined, widely used experimental tasks that are administered for both training and outcome measures, and which allow their implementation in a neuroimaging setting. This helps in interpreting the observed changes in neural functions and accounting for potential confounding factors (e.g., changes in sensorimotor processes or processing speed) that may also be affected by training (Salmi et al. 2018). Furthermore, most computerized EF interventions are relatively short, requiring ~20 sessions or less that are typically conducted over the course of a few days or weeks with minimal supervision. By contrast, more complex interventions (e.g., rehabilitation approaches in clinical settings, multimodal lifestyle, or educational interventions) typically take place over the course of months or even years, making them difficult to study using neuroimaging techniques.

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Neural Correlates of Executive Function Training: Getting at Underlying Mechanisms

Several groups have advanced our understanding of underlying mechanisms of EF training using functional and structural neuroimaging to test whether and how training might impact the prefrontal cortices and/or broader brain circuits (e.g., Salmi et al. 2018; Vartanian et al. 2022). Others have used electrophysiological measures or neuromodulatory approaches to answer this question. Since other chapters in this volume address those issues, we focus here on functional/structural neuroimaging using magnetic resonance imaging (MRI).

Since the year 2000, dozens of functional brain imaging studies, most of them conducted using functional MRI (fMRI), have examined the neural underpinnings of EF training by comparing brain activation before and after the intervention, and a few studies have also focused on capturing trajectories during the intervention (e.g., Finc et al. 2020; Kühn et al. 2013). Over the past several years, converging evidence has started to emerge. For example, a meta-analysis conducted by Salmi et al. (2018), provided systematic evidence that EF training modulates activity in distributed brain areas, encompassing prefrontal, parietal, sensory, and subcortical areas such as striatal nuclei. By comparing these EF training effects to training studies that rely on sensorimotor or language-related tasks, they found that some of the changes in brain activity—especially those involving PFC circuits—are shared across different types of training regimens despite the fact that the comparison interventions were not specifically designed to target EFs. The role of the PFC, however, seems to be particularly critical in EF training. These findings are consistent with domain-general models of learning, where EFs are at the top of the hierarchy, influencing general attention control processes and ultimately lower-level representational systems (Chein and Schneider 2005; see also Shiffrin and Schneider 1977). In other words, EF training can impact large-scale cortical and subcortical neural networks that facilitate both domain-specific and domain-general cognitive processes, with prefrontal circuits driving most of EF-related learning and brain plasticity.

Differential Training-Related Changes in Activation Patterns: The Role of Brain Region and Time on Task

Turning to the specific changes in activation patterns as a function of EF training, an early meta-analysis (Chein and Schneider 2005) found that in most brain areas, task-related activation amplitudes decrease from pre- to post-test, although subsequent work also provided evidence for training-related activation increases (Buschkuehl et al. 2012), which seem to be associated with shorter interventions. More recently, relying on a larger number of papers and including a wider range of interventions, Salmi et al. (2018) demonstrated that specific brain areas seem to respond differently to the effects of training. In particular, converging evidence from fMRI and positron emission tomography studies suggests that two critical areas along the frontostriatal pathways show complementary responses to training. More specifically, prefrontal activations seem to decrease over the course of training, while the activations tend to increase in subcortical areas associated with skill learning (Bäckman and Nyberg 2013). These findings are consistent with a growing number of behavioral studies reporting that positive training outcomes are at least partially explained by acquisition of strategies that help to off-load the demand on EFs (Dunning and Holmes 2014; Forsberg et al. 2020; Laine et al. 2018). In a more recent meta-analysis focused specifically on WM training studies, however, the only consistent finding was training-related activation decreases, especially with longer interventions (Vartanian et al. 2022).

The lack of consistent subcortical effects, and thus any evidence for activation increases, might be partially related to the fact that several studies have not been optimally designed to examine activations in these restricted nuclei, which should ideally be segmented individually in each participant. Nonetheless, given the extensive evidence of the role of the striatum in learning and EFs (Packard and Knowlton 2002), as well as its powerful anatomical positioning within a hierarchical multilevel mosaic system and importance in facilitating the integration of information across cognitive, reward and motor functions (Haber 2016), it is critical to further elucidate how this system contributes to malleability of EFs.

Another PFC-related neural circuitry where EF training effects have been observed in several studies is the cerebro-cerebellar system (see Salmi et al. 2018). As in the case of striatum, training-related changes in the cerebellum have been associated with support processes that off-load the demand on EFs and facilitate the automatization of processes that the brain can learn to anticipate (e.g., timing, sensorimotor integration, regularities in the stimulus contents) (Boyden et al. 2004).

Of note, training-induced changes are not only evident in brain networks, as shown by functional changes discussed above, they have also been shown to impact underlying neurotransmitter systems (e.g., Bäckman et al. 2011; Dahlin et al. 2008). Of particular interest here is the dopaminergic system, which is known to be involved in EF performance as well as more broadly in learning and plasticity (Bäckman et al. 2006; Brehmer et al. 2009). Critically, using PET imaging, it has been demonstrated that EF training-related changes are mediated by dopaminergic modulation of the PFC, especially in older adults (Bäckman and Nyberg 2013; Dahlin et al. 2008; Klingberg 2010; Salmi et al. 2018).

Although there is evidence from several studies that EF training leads to activation decreases in prefrontal circuits with increased training time, several studies point to differential activation patterns depending on the brain region as well as time on task (i.e., intervention length; Kühn et al. 2013) or type of intervention (Belleville et al. 2014). The inconclusive evidence thus far might be related to the fact that the vast majority of studies have focused on regional

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effects, which may not fully capture the plasticity of neural systems that respond to EF training and that are involved involved in modulating the functioning of other brain networks (Braun et al. 2015; Finc et al. 2020). In particular, changes in structural and functional connectivity are commonly observed after targeted EF training (Colom et al. 2016; Iordan et al. 2021; Thompson et al. 2016) and, importantly, functional connectivity seems to be one of the markers for learning outcomes (Faraza et al. 2021; Kundu et al. 2013).

Training-Related Changes in Brain Activation: What do They Mean?

While there is evidence for training-related changes in amplitude depending on brain region, time on task, or intervention type, the meaning of such decreases and increases has yet to be established. For example, practice-related activation decreases may reflect gains in "efficiency" such that behavior becomes more automatic and well established, which reduces the cognitive load (Neubauer and Fink 2009). Alternatively, participants might figure out different, more appropriate strategies over the course of the training (Forsberg et al. 2020; Laine et al. 2018), which might be reflected in the recruitment of additional (or different) networks (Buschkuehl et al. 2012). In particular, activation increases might reflect the implementation of novel, more EF-demanding strategies (Salmi et al. 2018). The compensation-related utilization of neural circuits hypothesis (CRUNCH) has been used to explain training-related changes in brain activation (Lustig et al. 2009). It proposes a nonlinear (i.e., quadratic) relationship between WM load and brain activation, which is particularly relevant in aging (Reuter-Lorenz and Cappell 2008). Aging leads to decreased neural efficiency which older adults can partially counteract by over-recruiting or over-activating relevant brain regions, at least at lower levels of cognitive load (i.e., "compensatory over-activation"; Festini et al. 2018). With higher cognitive loads, however, a resource ceiling is reached to limit neural recruitment, which in turn, leads to a drop in performance (Cappell et al. 2010). Research has shown that healthy older adults reach their resource ceiling at lower loads, compared with young adults, which is illustrated by a demand-activation curve that is shifted leftward (Cappell et al. 2010). Importantly, CRUNCH makes clear predictions about how activation in regions critical to EF should change due to training (Lustig et al. 2009). Specifically, training should simultaneously

- reduce activation under low cognitive load, consistent with the idea of reduced need for compensatory over-activation with training, and
- increase activation under high cognitive load, consistent with the idea of enhanced dynamic range of activation (i.e., greater responsivity under high demand) with training (Kennedy et al. 2017).

In other words, as shown in Figure 14.1a, with EF training, CRUNCH predicts a rightward shift of the demand-activation curve, irrespective of age (Festini et al. 2018). In line with CRUNCH, Iordan et al. (2020) demonstrated that

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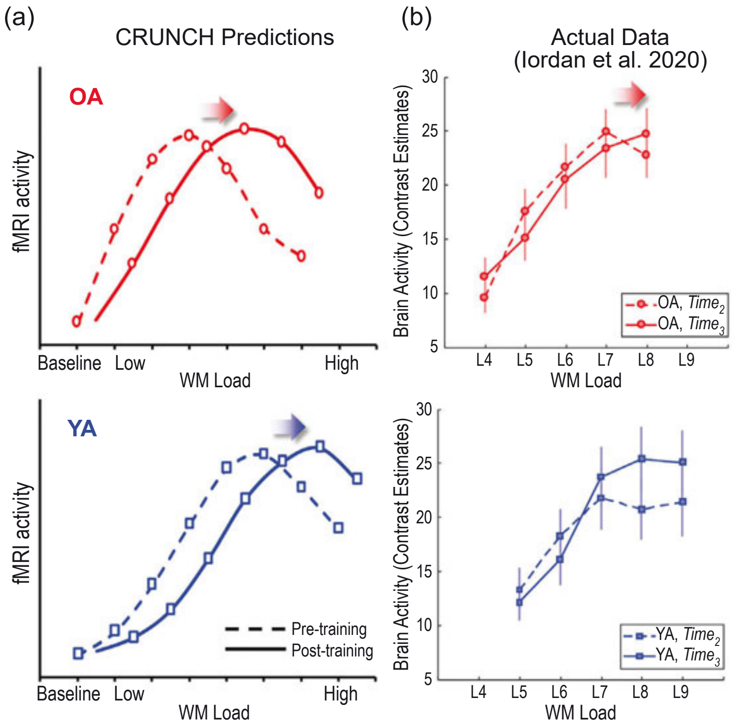

Figure 14.1 Hypothetical CRUNCH activation curves and supporting experimental data. (a) CRUNCH predicts a rightward shift of the neural recruitment curves with training, regardless of age. (b) Training effects in task-positive regions, associated with WM at baseline (Time 1), within each group. Both groups show greater activation at higher loads post (Time 3) relative to pre-training (Time 2). Panels reproduced from Iordan et al. (2020), with permission from Elsevier under a CC BY-NC-ND license.

training leads to activation increases in EF-related brain networks, specifically at higher memory loads, irrespective of age. Critically, training also shifts the demand-activation function rightward in older adults, consistent with a pattern of lower activation post- relative to pre-training for low cognitive loads, and greater activation post- relative to pre-training at higher cognitive loads (Iordan et al. 2020) (see Figure 14.1b). These results hold for both meta-analytically defined and age-group specific EF networks, comprising dorsolateral and ventrolateral PFC as well as lateral parietal cortices (Iordan et al. 2018, 2020, 2021).

Open Questions: Participant Motivation and its Role in Frontostriatal Plasticity

A critical aspect of neural mechanisms involved in EF training, which is still poorly understood, is the role of participant engagement and motivation.

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According to behavioral studies, there is evidence that these factors do predict training gains (e.g., Carretti et al. 2011; Jaeggi et al. 2011, 2014). Therefore, it would be important to provide a better understanding of how engagement and motivation to practice influence not only behavior, but also the prefrontal circuitries, and how to disentangle these effects from core EF training effects. Given the important role of frontostriatal networks in motivation (see e.g., Wise 2004), this could be a key target system to investigate the coupling between learning and willingness to learn which might contribute to further enhance the interventions' efficacy. The link between motivation and other cognitive processes is, however, not only an empirical but also a conceptual challenge (cf. Braver et al. 2014).

Executive Function Training in Populations With EF Deficits

The malleability of brain functions as a result of EF training has been studied in various clinical populations where EF deficits are part of the core pathology. Such populations include ADHD (Lambez et al. 2020), schizophrenia (Reser et al. 2019), depression (Woolf et al. 2022), substance use disorders (Caetano et al. 2021), obsessive-compulsive disorder (cf. Duncan and Friedman this volume), and various neurodegenerative disorders, such as multiple sclerosis (MS), or age-related disorders such as Parkinson disease, Alzheimer disease, and related dementias (Lasaponara et al. 2021).

A recent transdiagnostic meta-analysis highlighted the critical role of the striatum, anterior insula, and the PFC, arguing that these are the core regions underlying EF deficits occurring in various syndromes (Yaple et al. 2021). The fundamental issues for brain imaging studies to address in clinical populations include whether and to what extent the dysfunctional neural processes can be influenced with behavioral interventions, and if so, whether there are specific malfunctioning neural circuitries that respond particularly well to training, and how such responses are manifested. In other words, the question is: Does PFC circuitry need to be intact to benefit from targeted EF training? On the behavioral level, even though there are mixed findings in the literature, there is emerging evidence that EF training provides greater benefits to phenotypes that express deficits in EFs, such as individuals with ADHD compared to those who do not (Karbach et al. 2017; Traut et al. 2021). This emphasizes both the need and potential for interventions that target and optimize PFC circuitry (Salmi et al. 2020).

In Neurodevelopmental Disorders: ADHD

Even though the literature on neural correlates of EF training in neurodevelopmental disorders is still scarce, some preliminary evidence on the effects of EF training have been reported, mostly on prefrontal, parietal, and temporal activity. For example, in two early studies that focused on ADHD, functional (Hoekzema et al. 2010) and structural (Hoekzema et al. 2011) changes were reported following 10-day cognitive training interventions which tapped multiple EF domains. However, like two other studies (de Oliveira Rosa et al. 2020; Stevens et al. 2016), sample size was small and other experimental issues limited the interpretation of findings (e.g., lack of control group with ADHD, add-on stimulant treatment). Using a slightly larger sample size, Salmi et al. (2020) examined changes in regional brain activity from pre- to post-test in a randomized controlled trial with dual n-back WM training. By including a group of neurotypical adults to the pretest session, they first extracted brain activity that was aberrant in ADHD adults and then demonstrated that some of these deviations in brain activity were restored during the training period. In this study, Salmi et al. also demonstrated that the neural modulations for trained and untrained (transfer) tasks were in the opposite direction: In trained tasks, they observed decreased activity, whereas in the untrained variant of the n-back task, activity increased. These findings could partially explain why reports of training-related activation increases versus decreases have not been systematic in the literature. As mentioned above, there has been a lot of variability in the training protocols and outcome measures across EF training studies, both in neurotypical populations as well as in clinical studies (Pergher et al. 2020b; Tullo and Jaeggi 2022); even in healthy participants, only very few brain imaging studies have included both trained and untrained variants of the EF task in the pre- to post-test battery. Despite these methodological limitations, the loci of activations have been consistent across these few ADHD studies, as training-related modulations have been systematically observed in overlapping parts of the prefrontal, parietal, and temporal cortices, which are among the areas that typically show aberrant brain activity in this clinical group (Cortese et al. 2012).

In Neuropsychiatric Disorders

The literature on training-related plasticity is more extensive in other neuropsychiatric disorders, in particular, schizophrenia. Here, even though a majority of studies seem to observe increased activations in left prefrontal regions, summarized by Mothersill and Donohoe (2019), there is also evidence for a more widely distributed pattern of activation across cerebro-cortical and subcortical areas after training. At the same time, the authors point out the extensive heterogeneity of these findings, which they attribute to the broad range of interventions implemented, making it difficult to extract a consistent and statistically significant pattern.

Focusing on psychiatric disorders more broadly, a recent meta-analysis of brain imaging studies of EF training, Li et al. (2022) reported consistent activation increases in the left inferior frontal gyrus and decreased activation in the precuneus and cuneus, when comparing pre- and post-test. These findings are supported by earlier meta-analytic findings reported by Salmi et al. (2018), who focused on EF training in nonclinical participants. In other words, the same core brain regions seem to respond to EF training in both clinical and nonclinical populations; however, the direction of the effects (i.e., decreases or increases in amplitude) seems to differ depending on the population. In general, and similar to pharmaceutical treatments (Kirkland and Holton 2019), EF training might restore the aberrant activity to a normal range (see Salmi et al. 2020).

In Neurodegenerative Disorders

Although fewer neuroimaging studies are available in neurogenerative disorders such as Parkinson disease or MS, the pattern is similar to neuropsychiatric disorders in that there seem to be (a) training-related increases in prefrontal, parietal, and cerebellar activity (cf. Prosperini and Di Filippo 2019), and (b) increased connectivity in the frontoparietal network and the default mode network, as captured by resting-state fMRI. With respect to MS, Prosperini and Di Filippo (2019) concluded that current evidence related to EF training-induced plasticity is fragmented, and that more evidence is needed on what would be the optimal brain imaging techniques in detecting the neural alterations relevant to MS, and how optimally to implement the training intervention (e.g., type, intensity, duration, combining behavioral, pharmacological treatment). As in other clinical conditions, one of the key avenues is to search for methods that will enable us to predict an individual patient's response to rehabilitation.

In Healthy Aging

Given that the typical course of aging is characterized by a decline in the functioning of core EFs, older adult populations have become a frequent target of EF training. Several meta-analyses have focused on the neural correlates of EF training in healthy aging (Duda and Sweet 2020; ten Brinke et al. 2017), but work has also synthesized the neural correlates of EF training in mild cognitive impairment and dementia (Beishon et al. 2020; van Balkom et al. 2020). Collectively, this work further highlights the heterogeneity in the type of EF training and outcome measures used, as well as the wide range of imaging methodology and analysis approaches being implemented. Still, in general, there seems to be evidence for training-related changes in regional activity and functional connectivity in the prefrontal and parietal areas overlapping with those reported in MS studies (Prosperini and Di Filippo 2019). Beyond the results showing increased functional connectivity, there are findings of decreased connectivity after training (Beishon et al. 2020) as well as reports that demonstrate more pronounced segregation of frontoparietal and default mode brain networks after training in younger but not in older adults (Iordan et al. 2021). Similar to the issue of training-induced activation increases versus decreases,

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our understanding of the changes in the strength of the functional connectivity and topological patterns in the large-scale neural networks is still limited (Baniqued et al. 2019).

Summary

The effects of EF training on brain activity and connectivity in populations with impaired EFs seem to be in line with compensatory mechanisms (Lövdén et al. 2012), in particular, the CRUNCH model (Reuter-Lorenz and Cappell 2008). In this context, neural compensation refers to alterations in neural functioning that offset the effects of age-related neural decline or pathology and facilitate elevated levels of cognitive and behavioral output. Specifically, older adults or otherwise compromised individuals frequently show greater and more widespread frontal lobe activity and less functional network segregation (Iordan et al. 2020, 2021). Under conditions of equivalent cognitive performance, the interpretation is that additional activation and network integration may serve a compensatory function (Reuter-Lorenz and Cappell 2008; Reuter-Lorenz and Iordan 2018). When neural plasticity is compromised (e.g., due to more advanced neural decline or pathology), CRUNCH predicts that individuals with EF needs, relative to healthy controls, would show lower, flattened demand-activation curves within frontal regions, responding only to small cognitive loads. When training succeeds, CRUNCH predicts a potential recovery of activation in frontoparietal regions, with a leftward shift of the demand-activation curve (see Figure 14.1). Furthermore, emerging evidence suggests that EF training can remediate aberrant neural activity in various clinical conditions. At the same time, given the considerable heterogeneity of EF-related disorders as well as the extensive interindividual differences across patients, the question of who is likely to benefit from training and which factors mediate positive training outcomes are of particular importance from a clinical point of view and has begun to receive more attention in recent years (Tullo and Jaeggi 2022).

Conclusions, Outstanding Questions, and Implications

Current research on EF training in various clinical and nonclinical populations across the lifespan suggests that behavioral and neural effects differ as a function of the tasks, intervention length, or populations, as well as other variables related to individual differences. In particular, there is variability in training benefits with respect to both training-specific gains as well as transfer, suggesting that there is no "one-size fits all" approach for EF training. The most salient questions that need to be addressed in current and future research concern how to determine which type of training works for whom, and why (Jaeggi et al. 2011; Pahor et al. 2022).

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There are several avenues to address these issues; in particular larger sample sizes are needed to uncover and replicate the relevant individual-difference factors that mediate and moderate the training outcome (Ørskov et al. 2021; Pahor et al. 2022). Here, it could be beneficial for research groups to use common methods (e.g., intervention types, outcome measures) to facilitate the acquisition of larger and more diverse datasets and allow for generalization beyond individual experiments and labs (Pergher et al. 2020b). To test the impact on training outcomes, an alternative approach would be to pick participants selectively according to certain characteristics, such as populations with or without EF needs—e.g., young verus older adults, individuals with and without ADHD (Iordan et al. 2021; Salmi et al. 2020). The recent literature has increasingly focused on those issues, demonstrating the relevance of certain individual-difference factors, ranging from preexisting cognitive abilities to performance during training, personality characteristics or demographic variables, along with motivational factors (Katz et al. 2021; Ophey et al. 2020; Ørskov et al. 2021), biomarkers including brain modularity (Gallen and D'Esposito 2019), or genotype (e.g., Bellander et al. 2011; Feng et al. 2015; Hernes et al. 2021; Zhao et al. 2020).

For instance, brain network modularity has been proposed as a biomarker of intervention-related plasticity, with particular relevance for aging (Gallen and D'Esposito 2019). Specifically, whereas high pre-training modularity, particularly during resting state, may reflect a more "optimal" functional network organization that promotes cognitive improvements with training (e.g., Gallen et al. 2016; Iordan et al. 2018), older adults (as well as clinical populations) may be less able to increase network segregation with training, as an expression of overall diminishing neural plasticity (Park and Reuter-Lorenz 2009; Reuter-Lorenz and Park 2014). Another possibility is that modularity may be generally beneficial for cognitive functioning, and local declines in brain function due to aging or neurodegeneration may be compensated by a more integrated workspace.

At the behavioral level, we and others have demonstrated that baseline abilities are among the key predictors for training-specific benefits (Jaeggi et al. 2011, 2014). Interestingly, while some work has shown evidence for compensation effects (i.e., individuals with lowest initial performance gain most from training or, in other words, catch up to the others), other work has found evidence for magnification effects (i.e., the rich get richer phenomenon) (Jaeggi et al. 2011; Karbach et al. 2017; Ørskov et al. 2021). It is currently unclear whether those differences are attributable to specific populations (e.g., age or patient groups) or related to training paradigms and the outcome measures studied, or a combination thereof (Feng et al. 2023). Our research findings emphasize the importance of paying attention to participants' performance in the training task themselves, as well as whether and to what extent they improve in nontrained variants of the training tasks ("near transfer"). Specifically, in several studies, we have demonstrated that those who improve during training

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and/or improve in nearest transfer measures are also more likely to show far transfer effects (Jaeggi et al. 2011; Jaeggi et al. 2014; Pahor et al. 2022; Parong et al. 2022). The key issue here is to figure out how to engage participants optimally during the intervention so that they can reap the full benefits of the training. Here, we and others have emphasized the role of good game design, along with motivational features which take into account participants' interests and demographic backgrounds (Deveau et al. 2015; Pasqualotto et al. 2022). Overall, it seems critical to account for individual differences that might affect adherence and persistence with cognitive training interventions (Tullo and Jaeggi 2022; Tullo et al. 2023). We also need to get a better understanding of the cognitive and neural mechanisms underlying training success, as well as the extent to which they might change as a function of EF training (Gallen et al. 2016; Kühn et al. 2011; Pahor et al. 2022; Parong et al. 2022). Furthermore, it is important to recognize that there is considerable overlap between the PFC circuits engaged in task performance and those involved in motivation and effort (Braver et al. 2014; Haber 2016). This poses an interesting and unique challenge for EF interventions: the targeted skills are also (or closely related to) the abilities required to engage effectively with the intervention itself; this is especially salient in ADHD, where issues with motivation and persistence are part of the core symptoms (Arnsten and Rubia 2012; Shen et al. 2020; Sibley 2020). As such, the issue is whether the effectiveness of EF interventions might benefit from incorporating additional tasks or components that purposively engage motivation- and/or effort-related circuits. Indeed, some groups have started to implement such approaches, e.g., by adding metacognitive and/or motivational components with promising effects (e.g., Carretti et al. 2014; Jaeggi et al. 2023; Vranic et al. 2013).

Another approach to maximize training benefits by capitalizing on potential additive effects could include the combination of EF training with physical exercise (Daugherty et al. 2018; Karssemeijer et al. 2017), brain stimulation (Au et al. 2022), mindfulness meditation (Course-Choi et al. 2017), or by more broadly incorporating multidomain lifestyle factors, as demonstrated by the FINGER study (Rosenberg et al. 2018). Such approaches likely implicate brain regions beyond the PFC networks and thus might increase the likelihood for broader/generalized and possibly, more sustained effects. At the same time, it is important to keep in mind that such multimodal interventions are typically much more demanding in terms of time, logistics, and personnel as compared to unimodal interventions, and it is not always clear what components work best and in what combination. As such, getting a mechanistic understanding of the intervention efficacy is even more challenging.

In conclusion, emerging research points to the relevance of personalized training approaches that take into account participants' strengths and needs, which can be derived from their preexisting EF skills, as well as their demographics, personality, interests, and biomarkers (e.g., brain network modularity, genotype, dopaminergic functions). The cognitive training literature might

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benefit from taking inspiration from precision medicine (Lenze et al. 2021). Furthermore, getting a better understanding of the intervention-related factors and the ideal combination of intervention components is critical for the design of effective and sustainable interventions to benefit a broader range of populations.

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